



First External Release Draft Integrated Science Assessment for Lead

**Briefing for the
Materials of Evolving Regulatory Interest Team (MERIT)
Information Exchange Meeting
Department of Defense**

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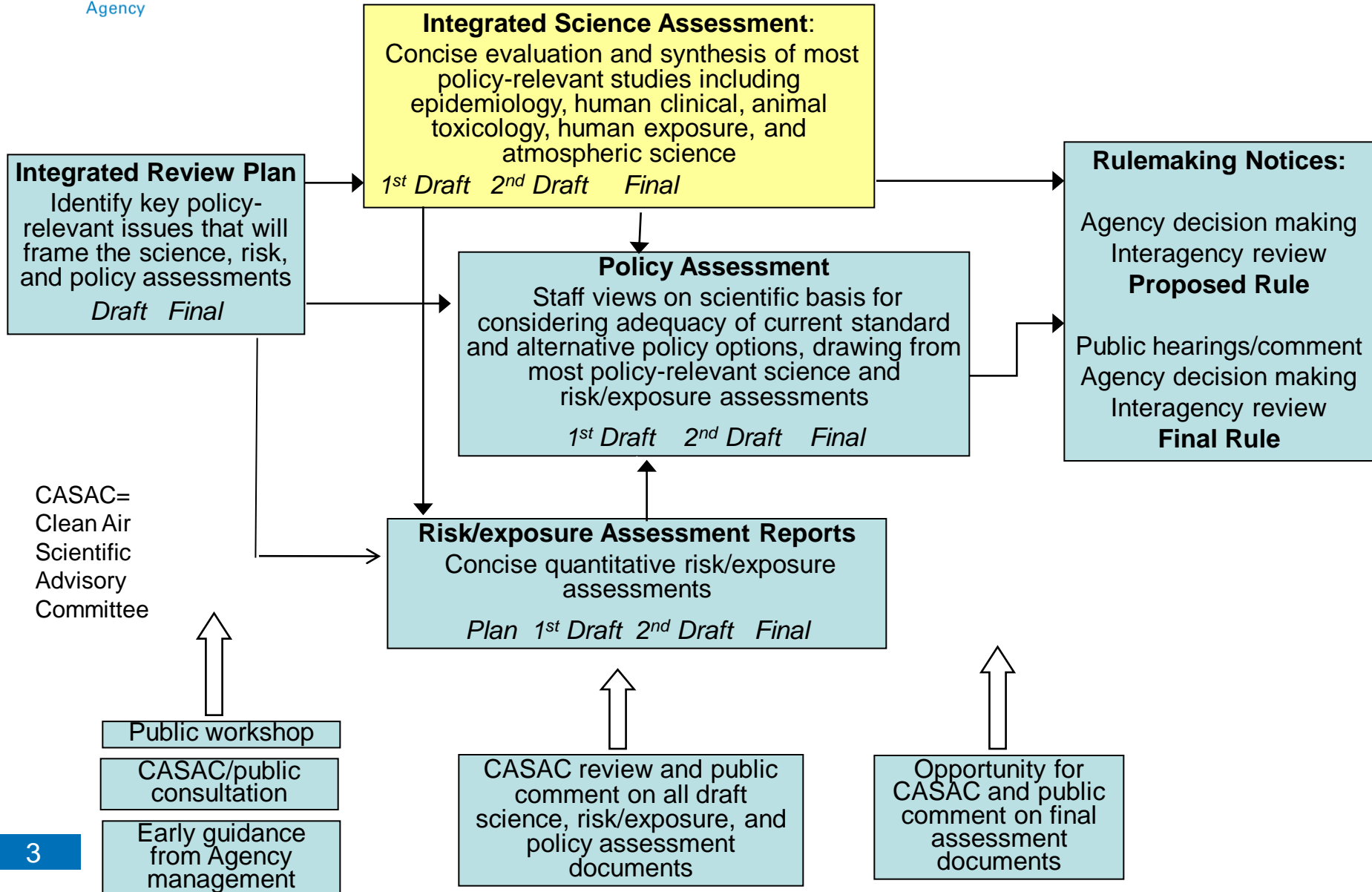
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National Ambient Air Quality Standards (NAAQS) Review Process



Timeline for Current Pb ISA

Science and Policy Issue Workshop	→	May 10-11, 2010
Peer Input Workshop	→	December 2-3, 2010
Internal EPA Review	→	December, 2010-April, 2011
1 st External Review Draft	→	May 6, 2011
CASAC Meeting	→	July 20-21, 2011
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Final ISA	→	July 2012 target

Chapters of the 1st ERD Pb ISA

Chapter 1: Introduction

Chapter 2: Integrative Health and Ecological Effects
Overview

Chapter 3: Ambient Pb Source to Concentration

Chapter 4: Exposure, Toxicokinetics, and Biomarkers

Chapter 5: Integrated Health Effects of Pb Exposure

Chapter 6: Susceptible Populations

Chapter 7: Ecological Effects of Pb

Summary of the Current and Previous NAAQS for Pb

Summary of National Ambient Air Quality Standards Promulgated for Pb during the Period 1978-2008				
Final Rule	Indicator	Averaging Time	Level ($\mu\text{g}/\text{m}^3$)	Form
1978	Pb in TSP	Calendar quarter	1.5	Maximum arithmetic mean concentration
2008	Pb in TSP	3 month rolling	0.15	Maximum 3-month rolling average

Between 1978 and 2005:

- 1986 AQCD for Pb and 1990 Staff Paper
Options for NAAQS level in the range of 0.5 – 1.5 $\mu\text{g}/\text{m}^3$
- No revisions proposed
- Parallel multi-program, multimedia effort in the Agency focusing on non-air sources of Pb as well as actions to reduce air emissions and bring more areas into compliance with the existing NAAQS for Pb

Framework for Causal Determination

Weight of Evidence for Causal Determination

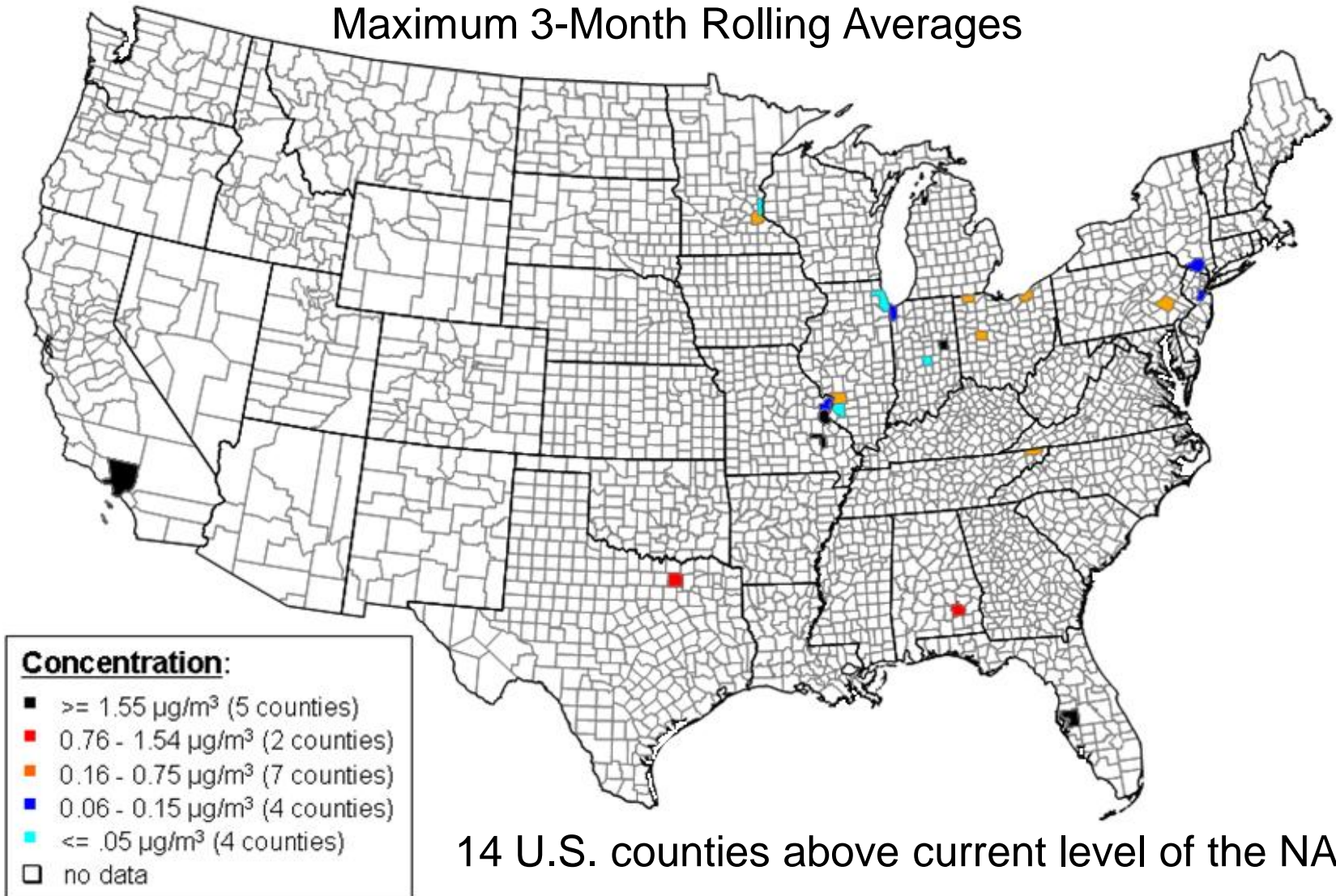
- Causal relationship
- Likely to be a causal relationship
- Suggestive of a causal relationship
- Inadequate to infer a causal relationship
- Not likely to be a causal relationship



United States
Environmental Protection
Agency

National Pb Concentrations

Source-Oriented[†] Pb Concentration, 2007-2009
Maximum 3-Month Rolling Averages



14 U.S. counties above current level of the NAAQS

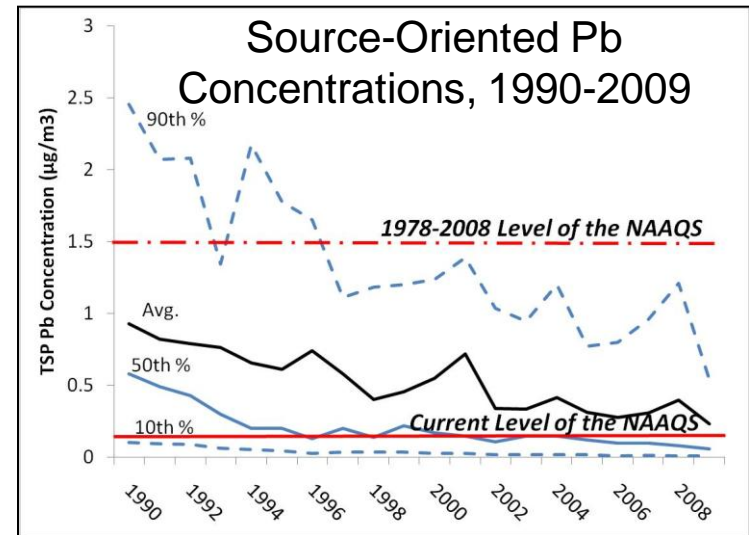
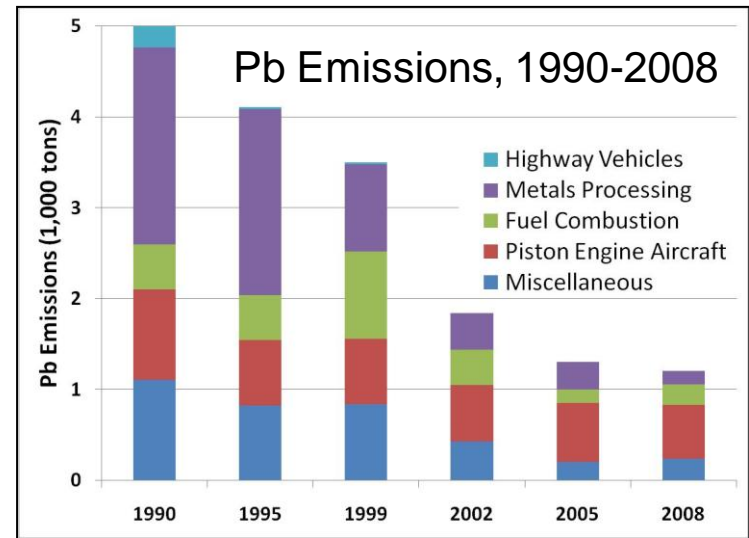
Trends in Ambient Pb

Emissions

- 77% decrease from 1990 to 2008
- Piston engine aircraft emissions comprise roughly half of all Pb emissions

Concentrations

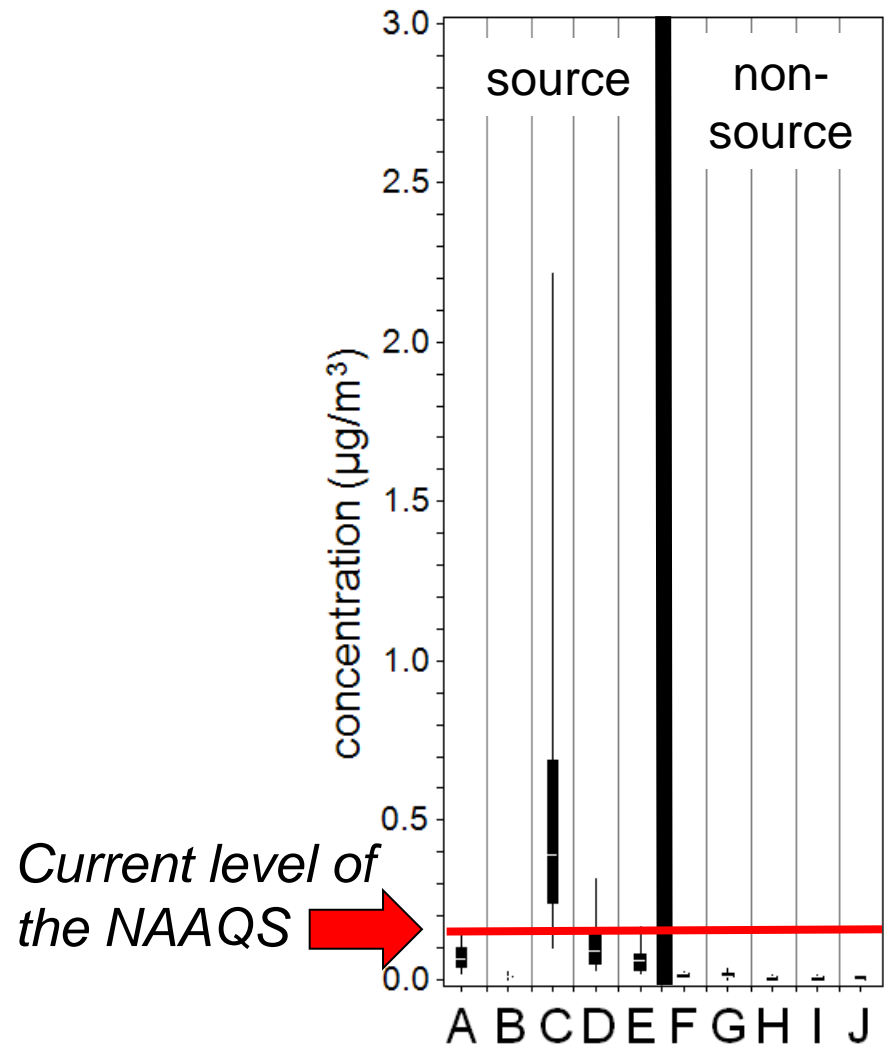
- Monitor metric: maximum rolling three-month average concentration
- Among source-oriented monitors: 2009 average is $0.23 \mu\text{g}/\text{m}^3$
 - Above the level of the NAAQS
- Among all monitors: yearly average decreased 78% from 1990 ($0.55 \mu\text{g}/\text{m}^3$) to 2009 ($0.12 \mu\text{g}/\text{m}^3$)



Monitor-specific Pb Concentration Distribution Source vs. Non-source

Los Angeles: 2007-2009

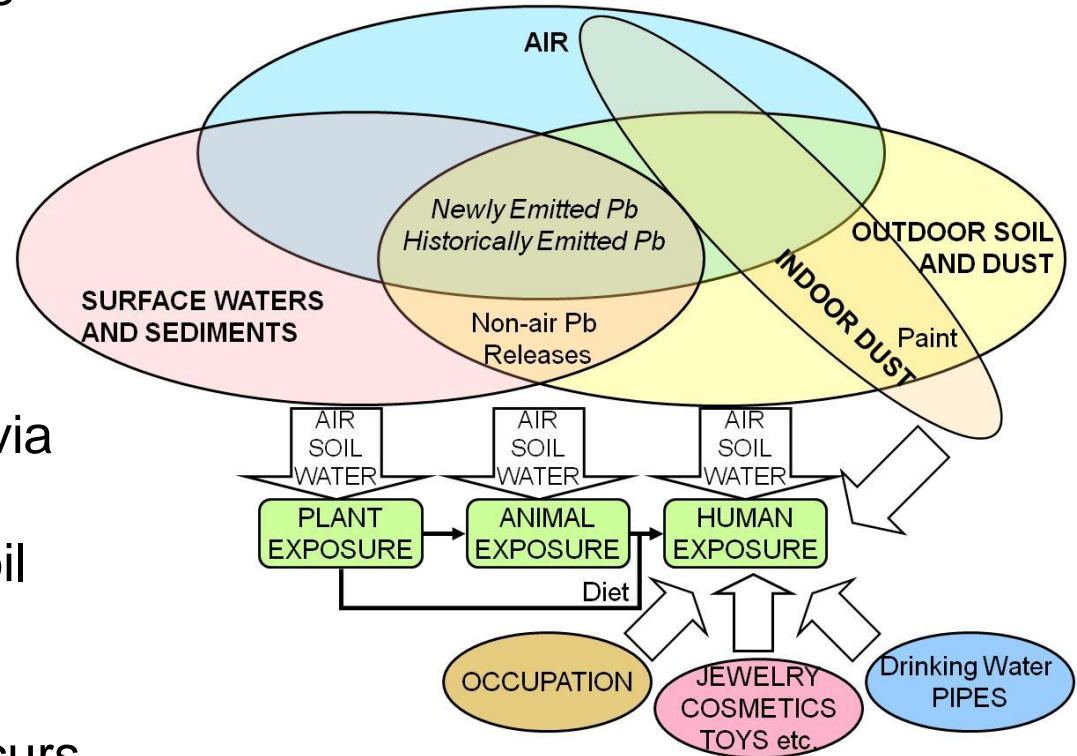
- Elevated concentrations near sources
 - Negligible non-source concentrations
- Concentration depends on:
 - Distance to source
 - Source strength
 - Wind speed and direction



Assessment Focus

Air-Related Pathways of Exposure

- Pb can cycle through multiple media before exposure
- Diagram illustrates complexity of exposure pathways
- Air-related exposure occurs via inhalation or ingestion of Pb contaminated food, water, soil or dust
- Non-air-related exposure occurs via drinking water pipes, occupation, consumer products



Pb Biomarkers

Bone

- 70-90% of Pb in body
 - Trabecular: 20% bone volume; highly perfused; slow Pb turnover (years)
 - Cortical: 80% bone volume; slower Pb turnover (decades)
- More rapid bone turnover in children than adults
- Increased turnover at times of increased physiological stress
- Generally an index of body burden and cumulative exposure

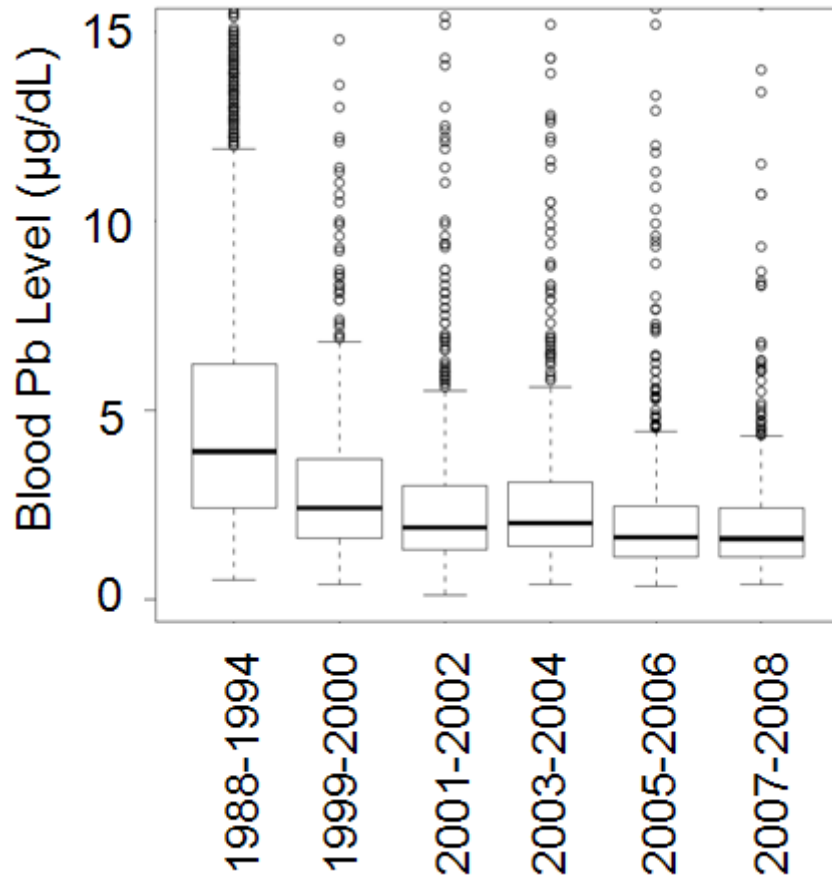
Blood

- Most commonly measured biomarker
- 1% of Pb in body
 - 99% bound to red blood cells
 - Pb in plasma thought to be more biologically active
- Generally an index of recent exposure in adults (months)
- Reflective of body burden in children due to rapid bone turnover

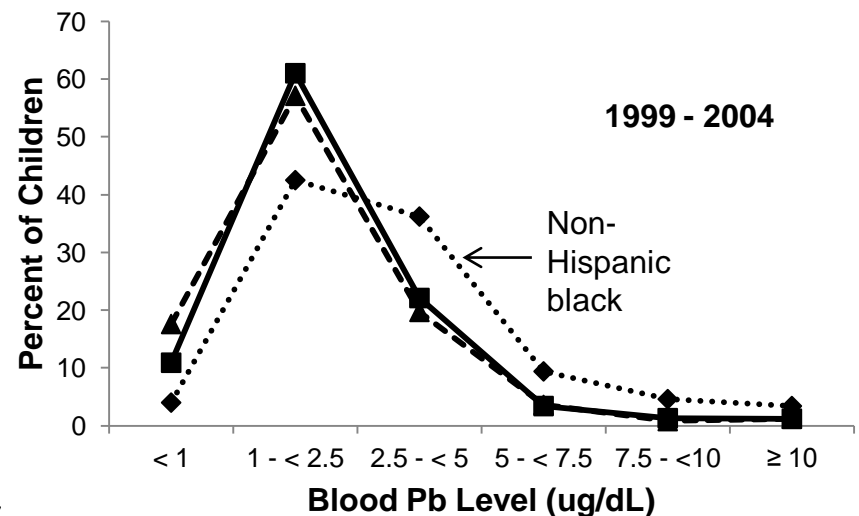
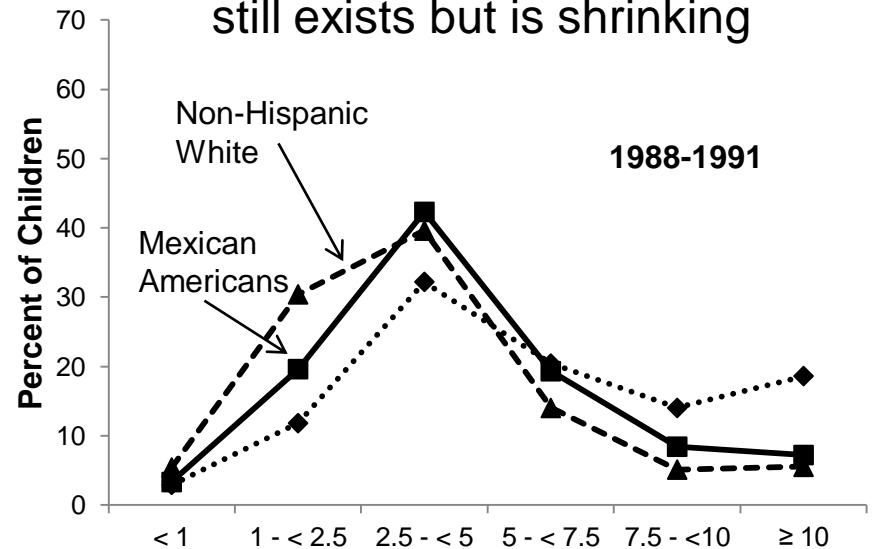
Trends in Blood Pb Levels

Children, Ages 1-5 Yrs.

Blood Pb levels are declining
across the U.S.



Gap among racial and ethnic groups
still exists but is shrinking



- On an urban basis, local disparities may be much larger

Sources: CDC (2010), Jones et al. (2009)

Blood Pb-Air Pb Slope

- Relationship between blood Pb and air Pb very important to 2008 NAAQS consideration
 - Industry supported a range of 3 to 7 $\mu\text{g}/\text{dL}$ per 1 $\mu\text{g}/\text{m}^3$ air
 - CASAC felt that 9 to 10 $\mu\text{g}/\text{dL}$ per 1 $\mu\text{g}/\text{m}^3$ air was more consistent with current conditions

Reference	Population, Location	Slope ($\mu\text{g}/\text{dL}$ per $\mu\text{g}/\text{m}^3$)
Schwartz and Pitcher (1989)	Children 0.5-7 yr, US	9.3
	Children 0-5 yr, Chicago	7.7
Hilts et al. (2003)	Children 0.5-6 yr, Trail, BC	6.5
Brunekreef et al. (1984)	Children, Various Countries	All: 6.1 ^A <20 $\mu\text{g}/\text{dL}$: 3.0 ^A
Hayes et al. (1994)	Children 0.5-6 yr, Chicago	5.7 ^A
Tripathi et al. (2001)	Children 6-10 yr, Mumbai, India	3.6
Ranft et al. (2008)	Children 6-11 yr, Duisburg, Germany	2.1 ^{A,B}
Schnaas et al. (2004)	Children 0.5-10 yr, Mexico City	1.1 ^A

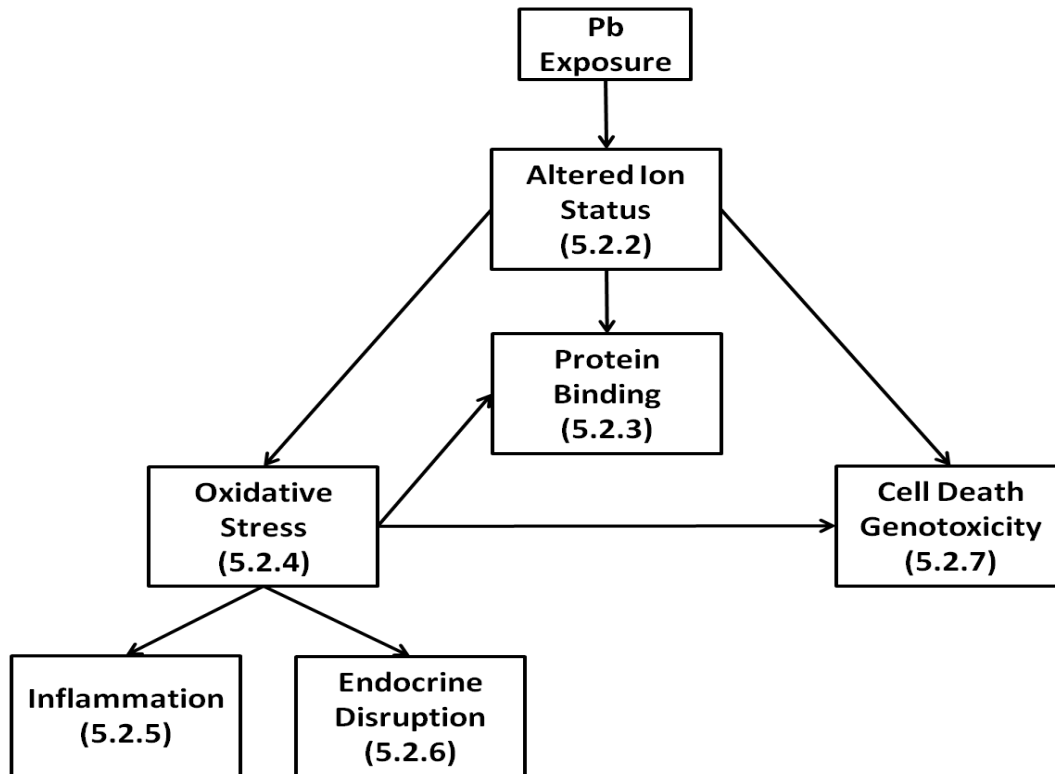
A – Non-linear model, slope calculated for air Pb of 1 $\mu\text{g}/\text{m}^3$

B - Adjusted for soil Pb concentration, which may reduce slope.

Health Effects of Pb Exposure

Outcome	Causality Determination
Nervous System Effects	Causal
Cardiovascular Effects (morbidity and mortality)	Causal
Renal Effects	Causal
Immune System Effects	Causal
Reproductive Effects and Birth Outcomes	Causal
Heme Synthesis and RBC Function	Causal
Cancer	Likely Causal

Modes of Action



- Pb-induced events upstream from observed health effects
- Multiple modes of action responsible for health effects
- Altered ion status is the major, unifying MOA

Modes of Action

Mode of Action	Related Health Effects	Lowest Level at which MOA Effects Observed
		Blood lead
Altered Ion Status	All Health Effects of Pb	3.5 µg/dL
Protein Binding	Renal, Hematological	6.4 µg/dL
Oxidative Stress	All Health Effects of Pb	5-10 µg/dL
Inflammation	Nervous System, Cardiovascular, Renal, Immune, Respiratory, Cancer, Hepatic	3 µg/dL
Endocrine Disruption	Reproductive and Developmental, Bone and Teeth, Endocrine System	2 µg/dL
Cell Death/Genotoxicity	Cancer, Reproductive and Developmental, Bone and Teeth	3.1 µg/dL

These levels of effect do not imply that these MOA are not acting at lower exposure levels, or that these doses represent the threshold of effect

Susceptible Populations and Lifestages

Factor Evaluated	Susceptible Population
Lifestage	Children
Sex	Outcome-dependent
Genetics	ALAD, VDR, DRD4, GSTM1, TNF-alpha, eNOS, APOE, HFE
Pre-existing Disease	Hypertension
Smoking	Smokers
Race/Ethnicity	Non-Hispanic Blacks, Hispanics
Socioeconomic Status	Low SES
Nutrition	Iron Deficiency
Stress	High Stress
Cognitive Reserve	Low cognitive reserve
Other Metals	Co-exposure to Cd, As, Mn

Susceptible Lifestages

Prenatal, Postnatal and Childhood

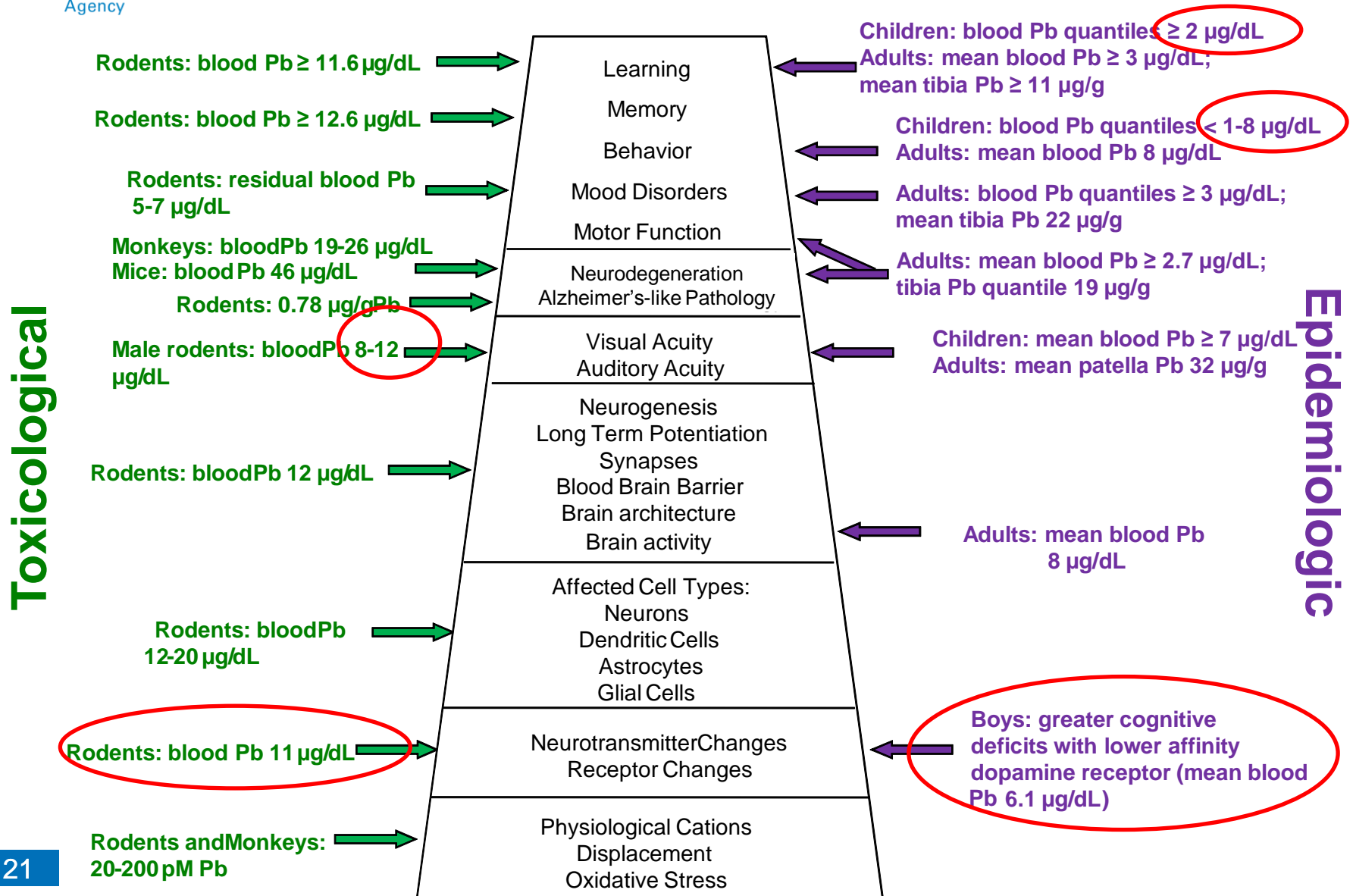
- Pb stored in bone is mobilized during pregnancy and lactation, increasing blood Pb levels
- Pb stores can be transmitted across the placenta *in utero* or through breastmilk from mother to infant
- Children's behaviors increase their exposure relative to adults (e.g. hand-to-mouth activities)

Susceptible Lifestages

Prenatal, Postnatal and Childhood

- CNS effects in children sensitive endpoint
 - Pb exposure may alter the normal course of morphogenesis and maturation that occurs *in utero* or in early life
- Limited capacity of the developing brain to compensate for cell loss so effects of early Pb exposure may be permanent
 - Possibly explaining why chelation therapy has failed to demonstrate significant improvements in cognitive performance in Pb-poisoned children
- High correlation among blood Pb measurements at different ages, difficult to distinguish among effects of Pb exposure at different lifestages in epidemiologic studies
- Early life exposures are associated with effects in adulthood

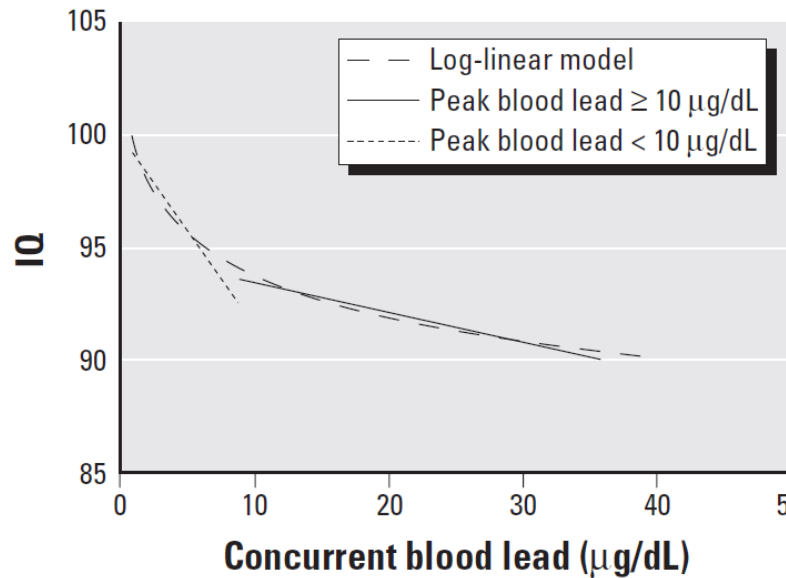
Nervous System Effects (Causal)



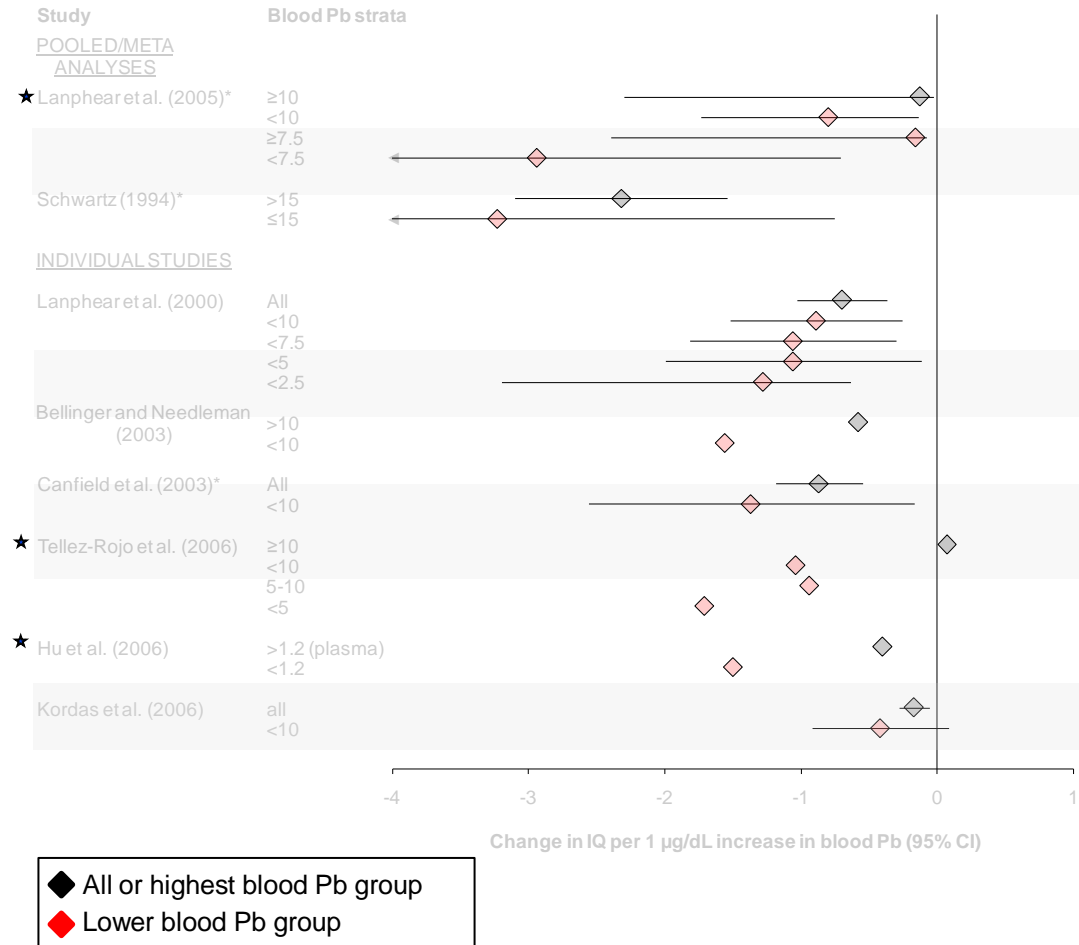
Red circles denote new evidence for additional endpoints or associations at lower blood Pb levels

Nervous System Effects (Causal)

Nonlinear association between blood Pb and cognitive function in children



Source: Lanphear et al. (2005)

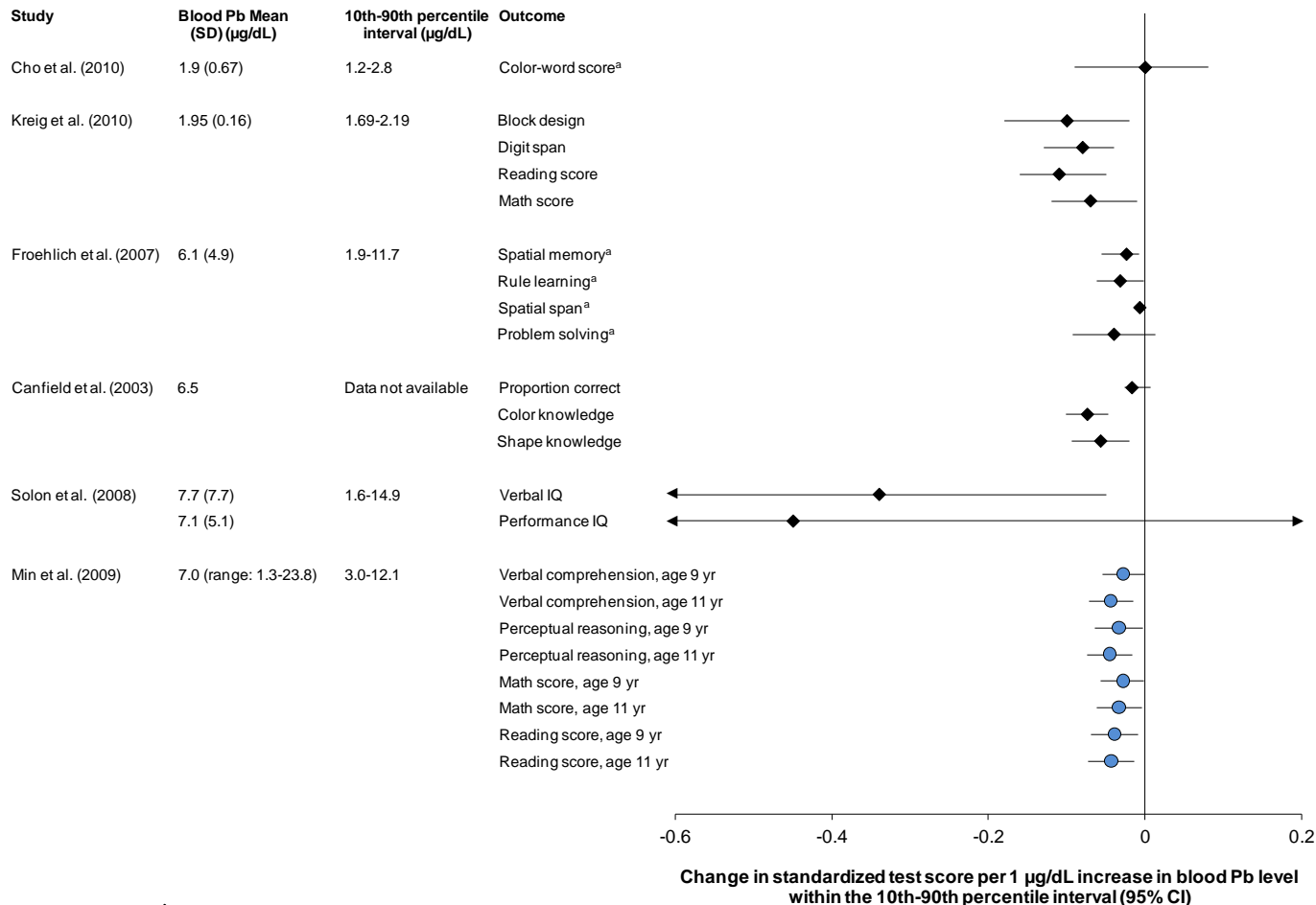


*Tested and found better fit for nonlinear model

★EPA-funded research

Nervous System Effects (Causal)

New evidence of association between blood Pb and cognitive function in children



- Children: associations at blood Pb levels 2-10 µg/dL

Supporting evidence

- Animals: in utero Pb exposure leads to deficits in learning and memory (blood Pb levels 2-13 µg/dL)
- Adults: associations with serial blood and bone Pb levels

Nervous System Effects (Causal)

- Behavior
 - Children
 - New evidence at lower blood Pb levels (~ 3 $\mu\text{g/dL}$) for inattention, hyperactivity, school problems, and delinquent behavior
 - New evidence for Attention Deficit Hyperactivity Disorder/diagnostic indices (blood Pb levels 1-2 $\mu\text{g/dL}$ and higher)
 - Adults: more evidence for anxiety, panic disorder, depressive disorder, criminal arrest
 - Animals: more evidence for impulsivity, increased response rates, depression, and emotional changes
- Continued evidence for effects in humans and animals on:
 - Auditory processing and hearing thresholds
 - Parkinson's Disease/neurodegeneration

Across nervous system endpoints

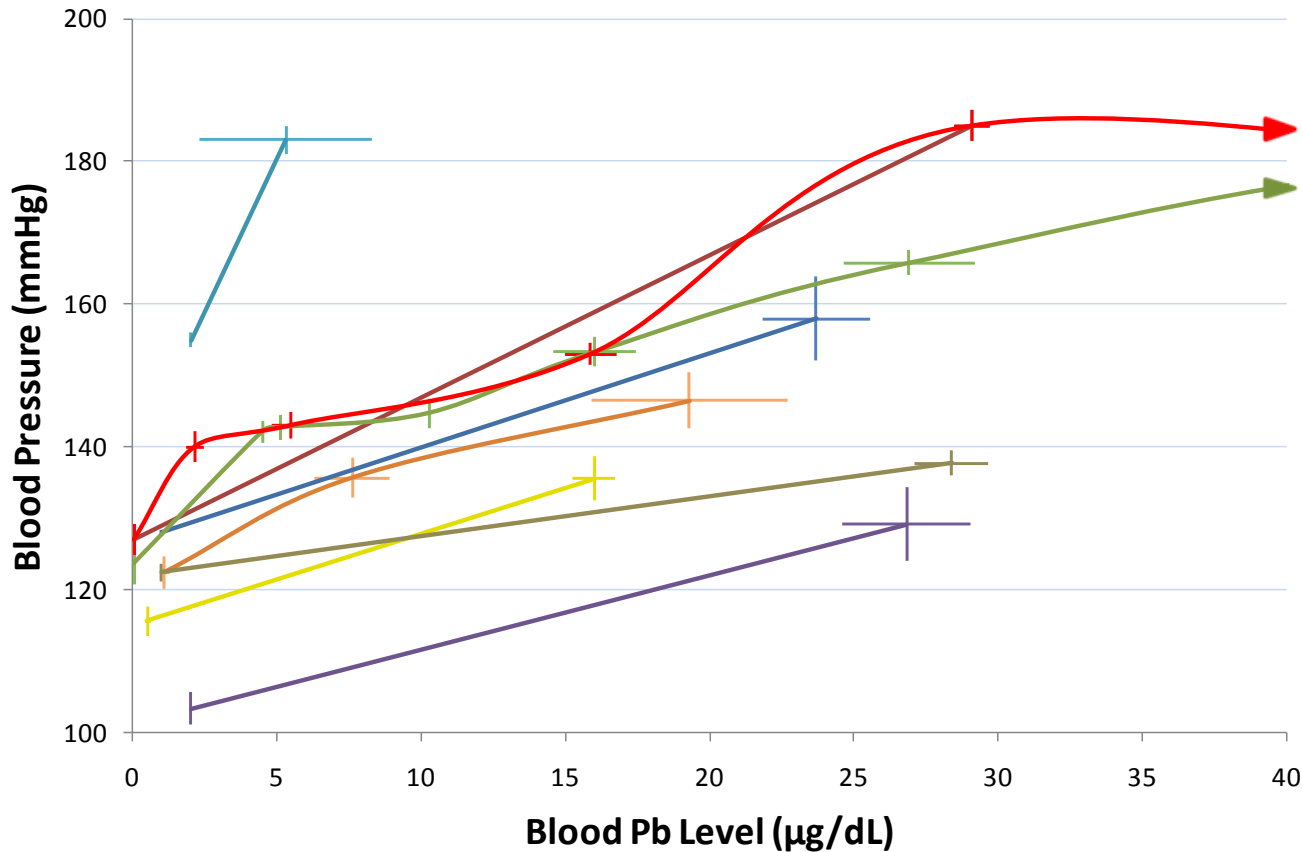
- Mechanistic evidence in animals for inhibited neurotransmitter release (e.g., dopamine), decreased synaptic plasticity, decreased neuronal differentiation, weakening of blood brain barrier
- New studies strengthen evidence for lack of a threshold in examined range of blood Pb levels (0.8 to > 10 $\mu\text{g/dL}$)

Cardiovascular Effects (Causal)

- New studies support findings from the 2006 AQCD of consistent relationships of concurrent blood Pb levels with blood pressure (BP) and hypertension
 - Previous studies: mean blood Pb levels 2-7 $\mu\text{g/dL}$
 - New studies: several studies with group blood Pb levels 1-2 $\mu\text{g/dL}$
- A new meta-analysis estimates a 1 mmHg increase in systolic BP and 0.5-0.6 mmHg increase in diastolic BP per 1 $\mu\text{g/dL}$ in blood Pb level
 - These associations may reflect effects of higher past Pb exposures
- Further evidence of association of bone Pb levels with increased BP and hypertension
- Blood Pb levels associated with development of other cardiovascular outcomes (e.g., ischemic heart disease, peripheral artery disease, heart rate variability)
- Toxicological evidence for oxidative stress, vasomodulation, hormonal dysfunction, and cellular damage provides biological plausibility for effects on blood pressure in animals and humans

Cardiovascular Effects (Causal)

- Animal studies show increased BP at blood Pb levels as low as 2 $\mu\text{g}/\text{dL}$
- Evidence for nonlinear concentration-response in multi-treatment studies (some evidence in humans)



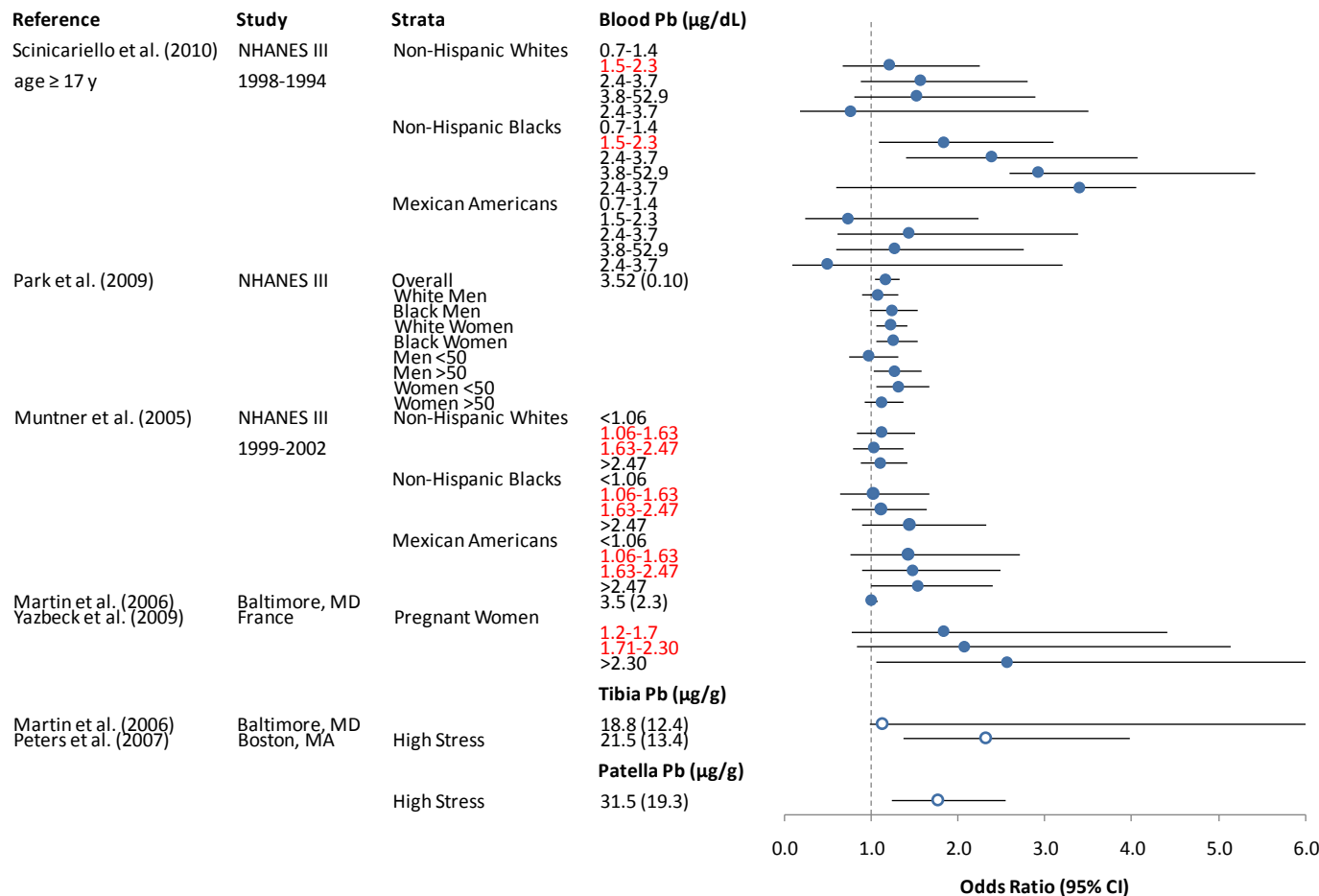
Changes in BP after Pb exposure in unanesthetized adult rats across studies. Crosses represent SE for blood Pb and BP measurements. If no crossbar is present, error results were not reported. Arrows represent higher doses tested.

Bravo et al. 2007 Chang et al. 1997 Chang et al. 2005 Heydari et al. 2006 Nakhoul et al. 1992
Rizzi et al. 2009 Rizzi et al. 2009 Tsao et al. 2000 Zhang et al. 2009

Cardiovascular Effects (Causal)

Odds ratio (95% CI) for associations of blood (closed circles) and bone (open circles) Pb with hypertension measures in new studies

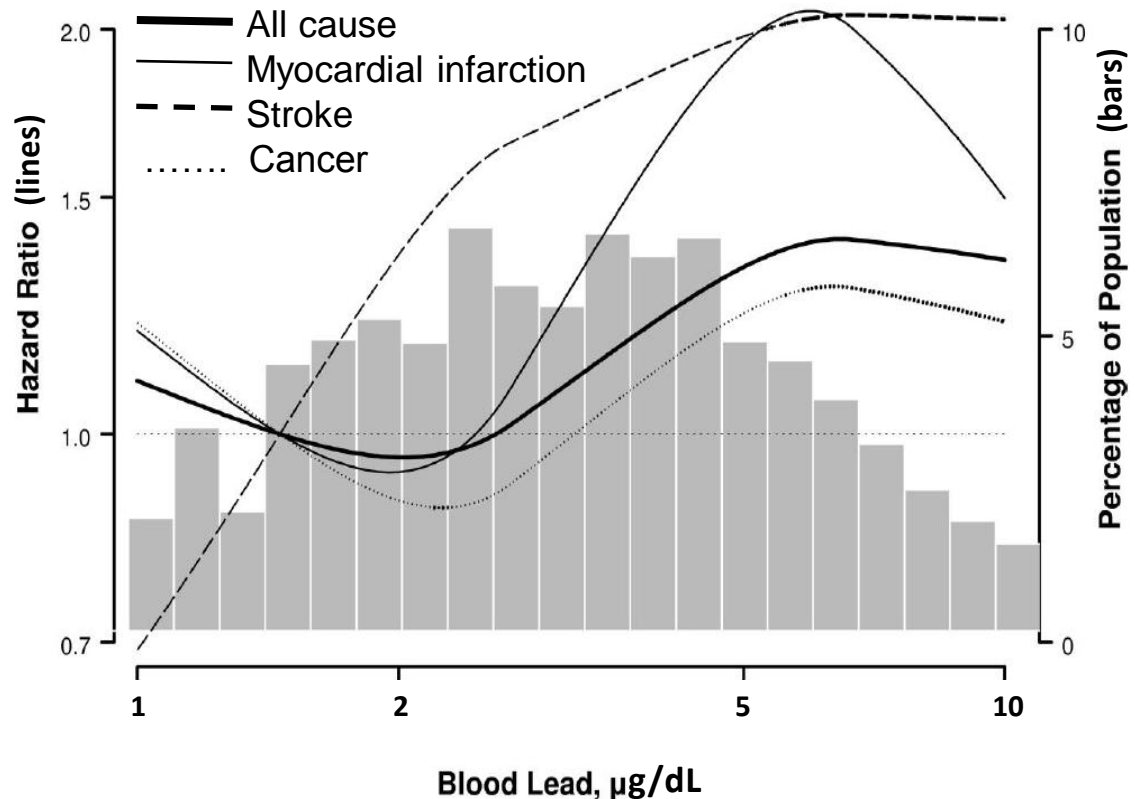
Positive associations at concurrent blood Pb >1.6 µg/dL



Cardiovascular Mortality

- New studies support and expand upon 2006 AQCD conclusions
- Greater Pb-associated risk for all-cardiovascular mortality and mortality from specific cardiovascular conditions (e.g., myocardial infarction, stroke, ischemic heart disease) than for all-cause mortality
- New evidence for associations between bone Pb level and mortality
- Recent NHANES (1988-1994) analysis found increased mortality at lower concurrent blood Pb levels (mean 2.58 $\mu\text{g}/\text{dL}$)
 - Maximal mortality risks at blood Pb 6-7 $\mu\text{g}/\text{dL}$
 - May indicate effects of higher past Pb exposures

Source: Menke et al. (2006)



Cancer (Likely Causal)

- Body of evidence consistent with that in 2006 AQCD
- Toxicology: Pb is genotoxic, clastogenic but at high doses
- Epidemiology: mixed results
 - Overall cancer incidence and mortality
 - Lung cancer, stomach cancer
- New findings for Pb-induced epigenetic changes
 - Implications for altered expression of DNA repair genes, tumor suppressor genes, oncogene

Lowest blood Pb levels at which effects are substantiated: Children

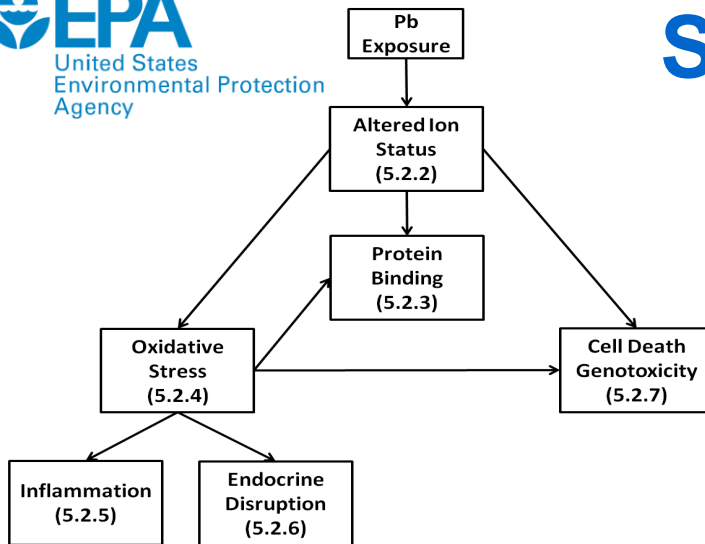
Observed Effect Blood Pb Level	Nervous System Effects	Reproductive Effects	Immune Effects	Effects on Heme and Red Blood Cell Function
20 µg/dL			Macrophage hyper-inflammation	
15 µg/dL			Lymphocyte activation	↑Zn protoporphyrin Lipid peroxidation
10 µg/dL	Delinquent behavior ↑hearing threshold			Altered antioxidant enzyme activities ↓aminolevulinic acid dehydratase activity ↓hemoglobin
5 µg/dL	Decrements in full scale IQ Inattention Decrements in specific neurocognitive domains Poorer school performance ADHD	Delayed Puberty	Increased B cell abundance Increased IgE Increased risk of infection Decreased T cell abundance	Decreased Ca-Mg ATPase activity (cell signaling)
1 µg/dL			Allergic sensitization	

Ecological Effects of Pb

New approaches in this ISA:

- Effects of Pb were reviewed from two perspectives: by system (terrestrial/aquatic) and by shared classes of effects
- Integration of human health and ecological effects of Pb (based on shared modes of action)
- Assessments at the species level were considered when evaluating causality at community and ecosystem scales
- Considered impacts to ecosystem services (the benefits people obtain from ecosystems)

Shared Modes of Action



The same Pb-induced upstream events that lead to observed human health effects are found in ecosystems

Mode of Action	Evidence in Biota
Altered Ion Status	Plants, Invertebrates, Vertebrates
Protein Binding	Plants, Invertebrates, Vertebrates
Oxidative Stress	Plants, Invertebrates, Vertebrates
Endocrine Disruption	Invertebrates, Vertebrates
Cell Death/Genotoxicity	Plants, Invertebrates, Vertebrates

Established Threshold Levels of Pb in Terrestrial Ecosystems

- In general, the obstacle to obtaining exposure-response information is strong interactions with other environmental factors (pH, cation exchange capacity, organic matter...) that modify both accumulation and effects
- Ecological soil screening levels (Eco-SSLs) are the maximum level that will not affect ecosystem receptors
 - Eco-SSLs have been developed by the EPA (2005) for screening purposes at Superfund sites
- Based on the most conservative assumptions:
 - Metal is in its most toxic form
 - Highly available
 - Highly ingested
- Eco-SSL values
 - Birds 11 mg Pb/kg soil (dry weight)
 - Mammals 56 mg Pb/kg soil (dry weight)
 - Plants 120 mg Pb/kg soil (dry weight)
 - Invertebrates 1700 mg Pb/kg soil (dry weight)

Established Threshold Levels of Pb in Aquatic Ecosystems

- Water quality criteria for Pb (1985) EPA Office of Water:
 - Freshwater maximum concentration: 65 µg/L
 - Freshwater continuous concentration: 2.5 µg/L
 - Saltwater maximum concentration: 210 µg/L
 - Saltwater continuous concentration: 8.1 µg/L
- Limitations of current water quality criteria:
 - Not updated since 1985
 - Does not account for considerable species differences in sensitivity to Pb
 - Only normalizes to water hardness, however, bioavailability is also determined by pH, dissolved organic carbon, alkalinity etc.

Effects Common to Health and Ecosystems

Outcome	Causality Determination
Neurobehavior: Invertebrates and Vertebrates	Causal
Developmental and Reproductive Effects: Invertebrates and Vertebrates	Causal
Hematological Effects: Invertebrates and Vertebrates	Causal
Physiological Stress: All Organisms	Causal

Ecosystem Effects

Outcome	Causality Determination
Bioaccumulation as it Affects Ecosystem Services: All Organisms	Causal
Mortality: Invertebrates and Vertebrates	Causal
Growth: Plants and Invertebrates	Causal
Growth: Vertebrates	Suggestive
Community and Ecosystem Level Effects	Causal

Neurobehavioral Effects (Causal, invertebrates and vertebrates)

- 2006 AQCD: Exposure shown to affect brain receptors in fish, organism behaviors (i.e., predator-prey interactions, competition and avoidance behaviors)
- New studies strengthen and add details to neurotoxicity findings:
 - Signaling pathways in catfish
 - Morphology of GABA motor neurons in nematodes
 - Inhibition of acetylcholinesterase in tadpoles
- Additional evidence for behavioral effects in lizards, pigs, fish, frogs and birds

Developmental and Reproductive Effects (Causal, invertebrates and vertebrates)

- 2006 AQCD: No information on reproduction in plants, limited evidence in invertebrates and vertebrates
- New studies in this review increase evidence:
 - Embryonic development effects in freshwater snails and rotifers
 - Multigenerational studies in soil nematodes, mosquito larvae
 - Delayed metamorphosis, skeletal malformations in frogs
 - Effects on steroid profiles and oocyte size in fish
 - Decreased testis weight in lizards
- In plants, information continues to be inadequate to infer a causal relationship

Hematological Effects

(Causal, invertebrates and vertebrates)

- 2006 AQCD: Decreased ALAD activity in invertebrates, vertebrates
- New studies have added to evidence of decreased ALAD activity
- Also, changes in RBC, WBC counts, altered serum profiles in some organisms

Physiological Stress

(Causal, all organisms)

- Physiological stress is indicative of overall fitness of an organism
- 2006 AQCD: Pb exposure may cause lipid peroxidation and changes in glutathione concentration
- There is now consistent and coherent evidence of upregulation of antioxidant enzymes and increased lipid peroxidation in algae, aquatic mosses, plants, gastropods, mussels, crustaceans, fish, amphibians and mammals

Mortality

(Causal, invertebrates and vertebrates)

- 2006 AQCD:
 - No information on plants, decreased survival in invertebrates and vertebrates
 - Younger organisms generally more sensitive than older ones
 - Invertebrates generally more sensitive than other taxa
- New evidence supports findings from the 2006 AQCD
 - Survival in a few species impacted at concentrations occurring near point sources
 - In plants, information continues to be inadequate to infer a causal relationship

Growth

(Causal, plants and invertebrates)

- 2006 AQCD: Decreased growth observed in algae, aquatic plants, soil invertebrates and aquatic invertebrates. Limited evidence in birds and mammals.
- In this review, additional evidence for decreased growth in plants and algae. Lowest EC_{50} for growth in *Chaetoceros* sp. (algae): 105 $\mu\text{g/L}$
- New evidence for growth effects in invertebrates at environmentally relevant concentrations
 - Juvenile freshwater snail (*Lymnaea stagnalis*) growth inhibition ($EC_{20} < 4 \mu\text{g/L}$).
 - Juvenile freshwater mussel, fatmucket (*Lampsilis silquoidea*): lowest genus mean chronic value ever reported for Pb (10 $\mu\text{g/L}$)
- In vertebrates, evidence is currently suggestive of a causal relationship

Community and Ecosystem Level Effects (Causal)

- 2006 AQCD: Most evidence of community and ecosystem level effects is near point sources. Effects of Pb difficult to interpret in those studies due to the presence of metals and other stressors. Evidence of trophic transfer in terrestrial and aquatic ecosystems, but without trophic magnification.
- New evidence in microcosm studies and field studies with other metals present
- Evidence for effects in soil and sediment-associated communities, specifically shifts in nematode communities and benthic invertebrates
- Shifts toward more Pb-tolerant genotypes and species, and declines in total number of species in aquatic and terrestrial plant communities
- Effects of Pb on mortality, growth, physiological stress, blood, neurobehavioral and developmental and reproductive effects at the species scale support causality for ecosystem scale effects

Timeline for Current Pb ISA

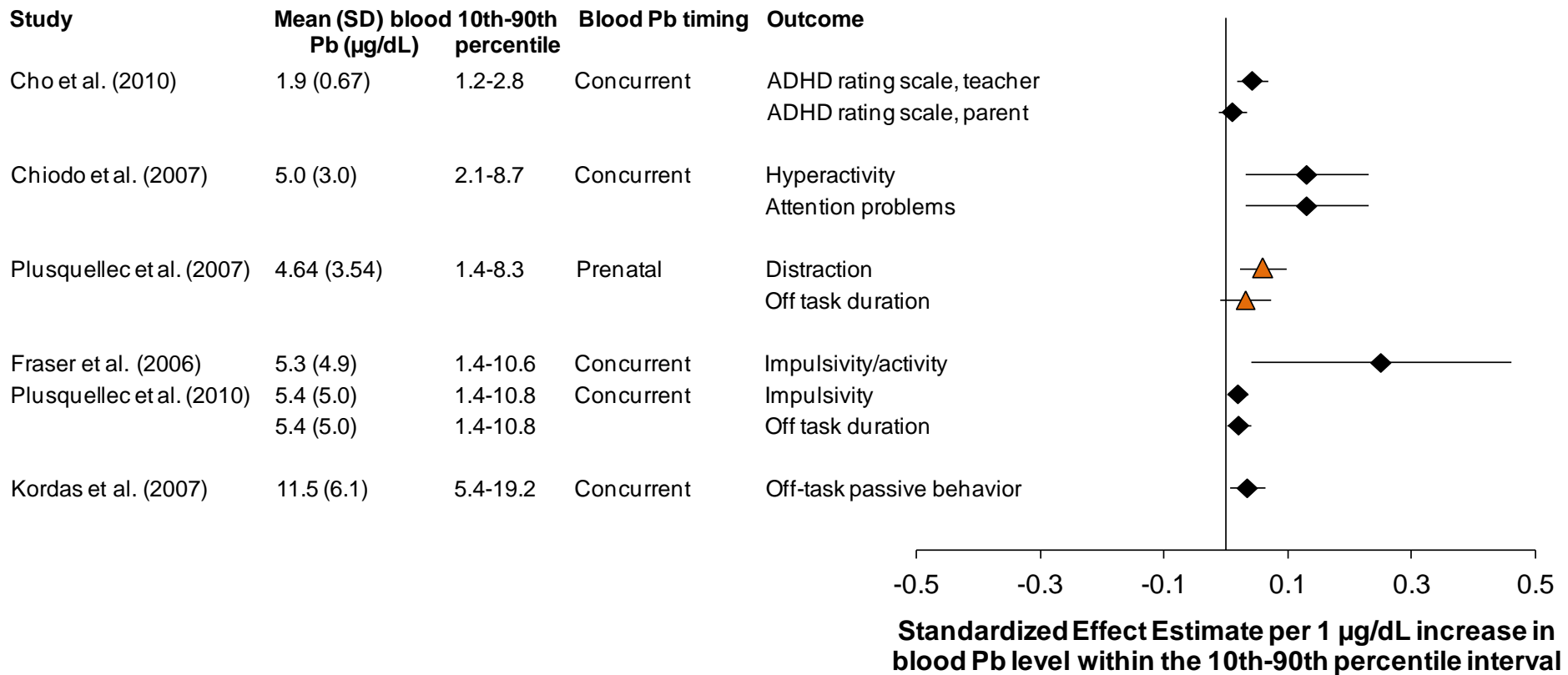
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Supplemental Material

Definition of Susceptibility

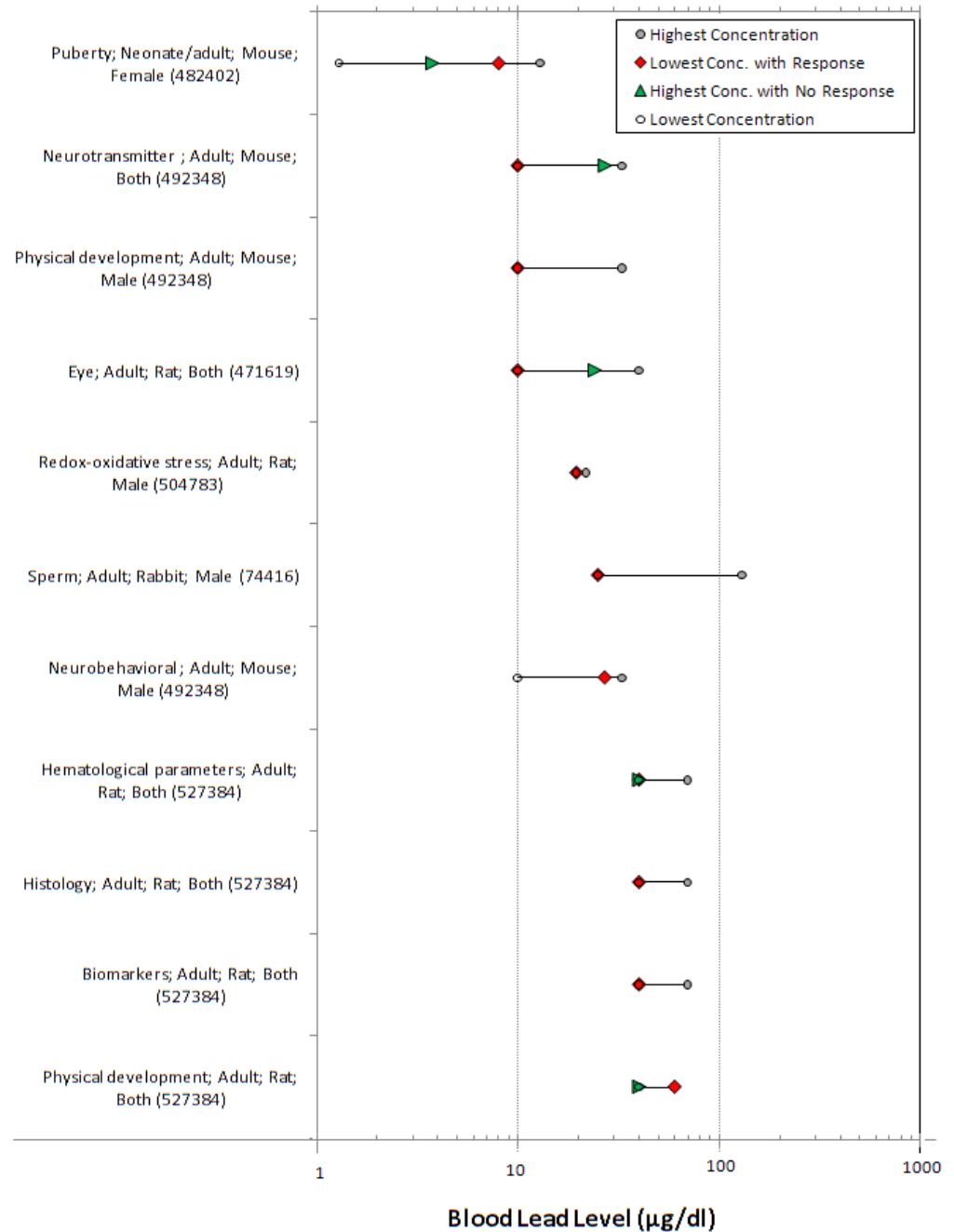
Individual- and population-level characteristics that increase the risk of Pb-related health effects in a population including, but not limited to: genetic background, birth outcomes (e.g., low birth weight, birth defects), race, sex, lifestage, lifestyle (e.g., smoking status, nutrition), preexisting disease, SES (e.g., educational attainment, reduced access to health care), and characteristics that may modify exposure to Pb (e.g., time spent outdoors).

Blood Pb level consistently associated with increases in behavioral problems in children



Reproductive Toxicology Effects

* These levels of effect do not imply that these MOA are not acting at lower exposure levels or that these doses represent the threshold of effect



Reproductive Effects (Causal)

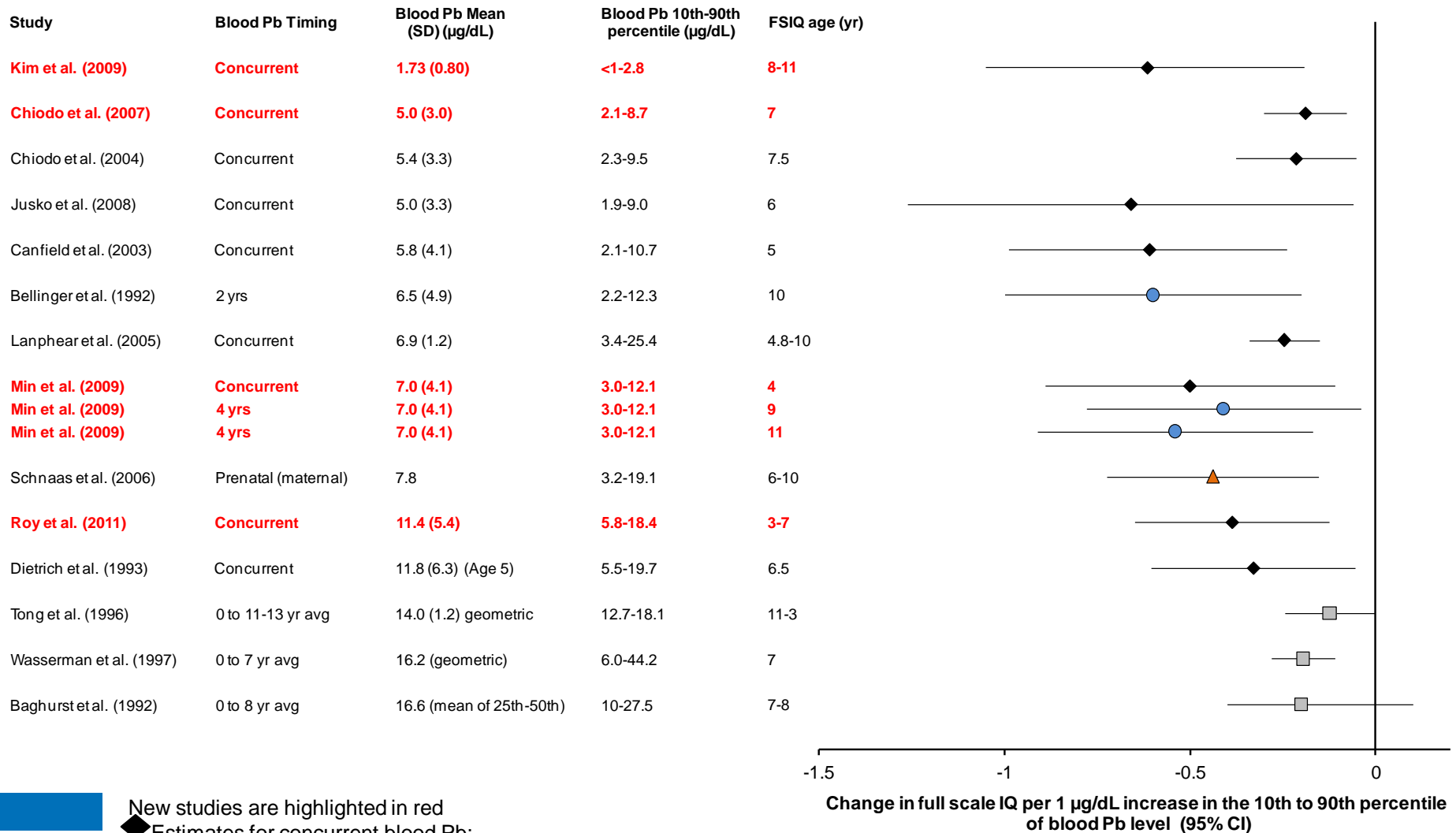
- Delayed Puberty Onset in Toxicology and Epidemiology Literature
 - males and females
- Significant effects on sperm
- Trans-generational effects with Pb exposure-toxicology and ecology
 - Ecology and toxicology effects in F1 and F2
 - Delayed growth (eco), delayed sexual development (tox, eco)
- Developmental outcomes (in utero, lactational exposure)
 - Retina & Auditory system
 - Obesity
 - Teeth
 - Skin
 - Liver and blood cells

Other Health Effects of Pb

- Renal Effects (Causal)
 - Consistent with 2006 AQCD
 - Increased serum creatinine and decreased creatinine clearance or GFR associated with blood Pb level ($<5 \mu\text{g/dL}$)
 - Renal effects in children observed (median $1.4 \mu\text{g/dL}$)
- Immune Effects (Causal)
 - 2006: Principal finding was shift from T helper type-1 (Th1) to T helper type-2 (Th2) responses
 - Continued toxicological evidence for \downarrow in Th1 cytokines and \uparrow in Th2 cytokines in T cells, new evidence in dendritic cells and new evidence in adults
 - Evidence for Th1 inhibition: \downarrow host resistance in animals, \uparrow prevalence of viral infections in humans (blood Pb levels $3\text{-}10 \mu\text{g/dL}$), \downarrow macrophage function in animals and humans
 - Evidence for Th2 stimulation: \uparrow immunoglobulin E (blood Pb levels $3\text{-}10 \mu\text{g/dL}$), more limited evidence for allergic sensitization and asthma in children (blood Pb levels $<2\text{-}10 \mu\text{g/dL}$)
 - Provides biological plausibility for increased inflammation in animals, in vitro models, and adults and for Pb effects in other organ systems (detailed in mode of action)

Nervous System Effects (Causal)

Associations between blood Pb level and full-scale IQ decrements in children



New studies are highlighted in red

◆ Estimates for concurrent blood Pb;

● Estimates for blood Pb measured earlier in childhood;

■ Estimates for blood Pb levels averaged over multiple years; ▲ Estimates for prenatal blood Pb levels